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Natural Products as Inspiration for the Development of Asymmetric Catalysis

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Abstract

Biologically active natural products often contain particularly challenging structural features and functionalities. Perhaps foremost among these difficulties are issues of stereochemistry. A useful strategy for synthesizing these molecules is to devise novel methods of bond-formation that provide new opportunities for enantioselective catalysis. In using this tactic, target structures define the problems to be solved and ultimately drive development of catalysis forward. New enantioselective methods discovered in the context of these total synthesis efforts then contribute to a greater understanding of fundamental bond construction and lead to valuable synthetic technologies useful for a variety of other applications.

Inasmuch as retrosynthetic analysis¹ enables synthetic planning toward valuable chemical substances, one can be easily discouraged by a lack of methods to install particular functionalities or structural motifs present in the target molecule. Still more difficult is adapting a strategic approach to incorporate the relatively limited number of *catalytic enantioselective* transformations to allow preparation of enantioenriched materials for further studies.^{2,3,4,5,6} However, when encountering the structural challenges presented by important natural products and pharmaceutical compounds a fruitful strategy is to design a synthesis that hinges upon a particular bond disconnection that is beyond the present lexicon of enantioselective transformations. Employing this strategy, the structures of target molecules provide the impetus for the development of novel transformations and lead to a greater fundamental understanding of methods of bond construction and catalysis. In this Review several recent examples of novel catalytic enantioselective transformations demonstrate the effectiveness of this useful strategy for the preparation of important structural motifs found in biologically active molecules. Each example has contributed not only an effective means of accessing a particular target structure, but also a useful new tool for a variety of further applications in synthetic chemistry.

To provide an overview of established catalytic enantioselective methods developed in the context of total synthesis, several notable examples are highlighted in Figure 1. In each of these cases, the target molecules posed particular challenges that had not yet been solved by enantioselective catalysis. Although in some instances (e.g., Diels–Alder reaction, Figure 1a) the methods were developed before their first applications in total synthesis, but the demonstrated value of the transformation served to further highlight the need for enantioselective variants. Subsequent to the development of the [4 + 2] cycloaddition by Diels and Alder in the 1920s,⁷ many studies of this transformation elucidated several key facets of

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the stereochemical outcome of the reaction (e.g., the “endo rule”, regioselectivity, and diastereoselectivity). These intrinsic stereochemical control elements proved useful when the Diels–Alder reaction was first featured in a total synthesis with Stork's stereocontrolled synthesis of cantharidin in 1951.⁸ Subsequently, the thermal Diels–Alder reaction found application in several total syntheses, perhaps most famously in Woodward's landmark synthesis of reserpine.⁹ Enantioselectivity in this transformation remained elusive, however, and perhaps was considered unattainable. One key practical improvement of the method was Yates' discovery that Lewis acids remarkably increased the reaction rate.¹⁰ Many laboratories sought to exploit Yates' discovery to develop asymmetric versions of the Diels–Alder reaction catalyzed by chiral Lewis acids, culminating with Koga's report of the first highly enantioselective catalytic Diels–Alder reaction in 1979.¹¹ The interface between reaction development, mechanistic study, and synthesis is readily apparent from the multitude of chiral Diels–Alder catalysts and accompanying enantioselective total syntheses reported to date.^{12, 13, 14} These successes validate the extensive efforts directed toward the realization of this important goal.

Other methods were developed to address more general synthetic problems (e.g., enantioselective ketone reduction, Figure 1a), however, these key structures are themselves embedded in a variety of important natural products and pharmaceutical compounds. In the case of Corey's approach to the prostaglandins, first reported in the 1960s,¹⁵ control of the configuration of the sidechain allylic alcohol at C(15) required stoichiometric chiral reducing agents until a solution to this long-standing problem was disclosed in the 1980s.¹⁶ Interestingly, the oxazaborolidine catalyst discovered in these explorations has found other varied applications in synthesis and catalysis^{13, 17} demonstrating the versatility of privileged molecular frameworks¹⁸ in enantioselective catalysis.

The practical impact of enantioselective catalysis is apparent in myriad industrial applications (e.g., Figure 1b–d) where the limits of catalysis must be examined in order to minimize costs. Important industrial applications include synthesis of chiral building blocks (e.g., amino acids, Figure 1b¹⁹), novel biologically active pharmaceuticals (e.g., Crixivan[®], Figure 1c²⁰), and commodity chemicals with various important uses (e.g., menthol, Figure 1d²¹). Only the most efficient methods are feasible for large-scale industrial synthesis and in many ways these protocols represent the zenith of modern enantioselective catalysis.^{22, 23, 24} A viable commercial operation must account for more than effective asymmetric induction; factors including turnover frequency, catalyst availability, catalyst recovery, catalyst toxicity, and feasible large-scale handling procedures must all be considered for industrial applications. These daunting challenges serve to further underscore the persisting demand for evermore efficient catalyst systems.

To maximize the utility of the stereochemistry imparted by these key asymmetric transformations, subsequent diastereoselective reactions may be used in order to control the formation of many stereocenters based on a single enantioselective transformation (e.g., Figure 1e). The Hajos–Parrish ketone, first prepared in the context of steroid synthesis, has been used extensively in other synthetic efforts, proving to be a versatile chiral pool starting material based on a variety of diastereoselective transformations developed around this versatile bicyclic platform.^{25, 26, 27} Interestingly, the amino acid catalyst system developed for this intramolecular aldol condensation provided a sound basis for the recent use of organic molecules as catalysts for a variety of enantioselective transformations (*vide infra*).

The use of several different enantioselective reactions to prepare enantioenriched fragments of complex molecules enhances efficiency through convergency. The importance of this strategy is shown in the variety of extraordinarily complex polyketide natural products that have been prepared through asymmetric intermolecular aldol reactions (e.g. phorboxazole B,

Figure 1f²⁸). The challenging structure of these molecules has required the development of several related protocols to address the subtle differences in substitution patterns and functionality present in substrates, and despite many successes, studies are ongoing.²⁹ Indeed, polyketide natural products exemplify the continuing need for reaction development in order to address stereochemically complex substructures.

The remaining examples in this Review detail recent representative developments of this paradigm for the construction of biologically important target molecules. Most of these involve the formation of C–C bonds, which compose the fundamental structure of organic molecules. These cases were selected to illustrate some of the latest developments in enantioselective catalysis for complex molecule synthesis. Special attention has been given to reactions that address some of the most significant challenges to synthetic chemistry today: increasing functional group tolerance, generating new carbocyclic- and heterocyclic-rings, and forming all-carbon quaternary stereocenters. The examples are intended to demonstrate the important symbiosis between total synthesis and method development and to show that improvements in one branch of synthetic chemistry can have a great impact in another.

β-Enamino Amide Hydrogenations – Januvia®

Throughout more than forty years of development, catalytic enantioselective hydrogenation has become one of the most effective and powerful methods for the synthesis of chiral α-amino acids for numerous applications.¹⁹ Over the past decade, the utility of their homologous building blocks, β-amino acids, in pharmaceutical, agrochemical, β-peptide, and natural substances has highlighted the need for a general and effective means of their preparation.^{30, 31} Undoubtedly, the implementation of a catalytic, asymmetric hydrogenation *N*-acyl-β-enamino esters seemed to be the most efficient pathway toward their synthesis, although initial investigations realized poor selectivities.³² Additional syntheses utilizing the chiral pool, auxiliaries, and more recently the catalytic, asymmetric generation of C–C and C–N bonds, have been successful in satisfying the increased demand for β-amino acids.³¹ These valuable methods enable flexible strategies for the synthesis of a variety of analogues; however, most examples are limited by the requirement that further chemical manipulation is often necessary to reveal the functionality of the desired β-amino acids.

Despite initial difficulties, the asymmetric hydrogenation of *N*-acyl-β-enamino esters has been developed into a useful method over the past 15 years.^{33,34} This fruitful endeavour has demonstrated that a number of transition metal and ligand combinations are competent for the preparation of *N*-acyl-β-amino acids with good to excellent enantioselectivities. A notable drawback to this strategy, however, is the requirement of the seemingly indispensable *N*-acyl group on the β-enamino esters, which enables metal chelation to improve reactivity and selectivity. The introduction of this moiety often produces enamine olefin isomers that can be difficult to separate, and importantly, the individual isomers are typically hydrogenated with differing rates and selectivities. Moreover, these difficulties were magnified by the necessary removal of this group, a seemingly cumbersome artifact of an otherwise powerful strategy. Nonetheless, this has enabled the preparation of a variety of β-amino acids.³¹

An innovative solution to this problem was demonstrated by a Merck group en route to Januvia® (sitagliptin phosphate, **8**, Figure 2), a recent FDA-approved treatment for type II diabetes mellitus.³⁵ The optimal target contains an unfunctionalized β-amino amide, and thus a strategy was sought to install this moiety directly by means of an asymmetric hydrogenation of unsubstituted β-enamino ester and amide derivatives (e.g., **4**).³⁶ A traditional hydrogenation route to amino acids is a proven, cost-effective method for the synthesis of chiral building blocks, and the industrial infrastructure is already in place to realize this goal, however, reduction of unprotected β-enamino acids was not effective with existing chiral catalysts. A

critical element to address such limitations is Merck's high-throughput screening facility, a platform technology to rapidly screen catalyst structures and reaction conditions, an essential component for the success of any catalytic, asymmetric process.³⁷ One potential complication for this hydrogenation strategy was avoided when it was observed that the preparation of the β -enamino ester and amide (e.g., **3** \rightarrow **4**) substrates proceeded with complete selectivity for the (*Z*)-isomer, presumably due to hydrogen bonding in the products.

A survey of transition metals and ligands revealed that rhodium complexes of the Josiphos (e.g., **5**) family of ligands efficiently catalyze the hydrogenation of a variety of substrates in high yields with excellent enantioselectivities. The remarkable functional group tolerance of this catalyst enabled the strategic implementation of this asymmetric transformation as the penultimate step of the synthesis, thereby maximizing the utility of the process and materials. Thus, phenylacetic acid derivative **1** was converted into β -ketoamide **3** in a one pot procedure via acylation of Meldrum's acid, followed by treatment with triazole salt **2** (Figure 2).³⁸ Exposure to ammonium acetate converted this into β -enamino amide **4** as a single enamine isomer. Hydrogenation of **4** in the presence of 0.30 mol% of rhodium(I) and ligand **5** provided β -amino amide **7** in >95% conversion and 95% enantiomeric excess (ee). Subsequent recrystallization and salt formation with phosphoric acid gave Januvia® (sitagliptin phosphate, **8**). Efforts to optimize efficiency and examine the mechanism of the asymmetric process revealed a reactivity and selectivity dependence on the pH of the reaction solution.³⁹ It was found that ~1 mol% of a mild acid (i.e., ammonium chloride) was essential for the reaction to proceed reproducibly on large scale. Additionally, it was observed that hydrogenation of a related substrate under identical conditions with a D₂ atmosphere resulted in deuterium incorporation at the β -position only, suggesting the intermediacy of an imine (i.e., **7**) and that an enamine/imine tautomerization process plays an important role in the mechanism.³⁶ Interestingly, intermediates such as **7** share a striking similarity to asymmetric β -carbonyl hydrogenations pioneered by Noyori.⁴⁰

This example demonstrates the evolution of asymmetric catalysis to a state of the art science through efficiency by minimization of unnecessary functionality, atom economy, and extremely active catalysts. Moreover, the development of the catalyst system for the synthesis of Januvia® exemplifies the continued need for subtly different catalysts to meet new synthetic demands. Building on the experience attained during the development of highly efficient enamide reduction toward α -amino acids, large-scale industrial synthesis of increasingly important β -amino acids has been a relatively rapid process.

C(sp³)-C(sp³) Cross-Couplings – Fluvirucinine A₁

Transition metal-catalyzed cross-coupling reactions have been used extensively for the construction of C-C bonds, and consequently have had a substantial impact on the field of complex molecule synthesis.^{41,42} The predominance of palladium and nickel catalysts in cross-coupling technologies and their extraordinary functional group tolerance increases the efficiency of this process through convergency by allowing a large degree of functionalization prior to coupling. Moreover, the efficacy of this cross-coupling strategy for streamlining synthesis has enabled retrosynthetic analyses previously thought impossible with standard, non-metal reactions. Until recently, however, the majority of cross-coupling methods involved C(sp²)-C(sp²) or C(sp²)-C(sp) centers, limiting the application potential. Two critical issues associated with expanding the substrate scope to include C(sp³)-C(sp³) couplings are the relative low reactivity of alkyl halides toward oxidative addition, and the propensity of σ -alkyl organometallic complexes to undergo rapid β -H elimination reactions.^{43,44} Practical solutions to this problem were first presented by Suzuki and Knochel, followed more recently by Fu and others.^{44,45} In general, the reaction scope now encompasses a variety of primary and secondary halides and pseudohalides as the electrophilic component with organoboranes,

boronic acids, alkylmagnesium halides, and alkylzinc halides as the nucleophilic component.⁴⁴ Although perhaps not developed in the context of a particular target molecule, progress in these cross-coupling methods has allowed retrosynthetic disconnections that were not practical previously. Asymmetric cross-coupling protocols could in turn enable the direct formation of remote stereocenters in relatively unfunctionalized molecules.

Early examples of catalytic, asymmetric cross-coupling reactions involving $C(sp^3)-C(sp^2)$ centers explored by Kumada and coworkers in the late 1970's were met with modest enantioselectivities.^{46,47} Despite these initial reports and the subsequent evolution of cross-coupling methods and asymmetric catalysis, a deficiency in the development of catalytic, asymmetric methods for $C(sp^3)-C(sp^3)$ couplings existed until Fu and coworkers reported an asymmetric Negishi coupling in 2005.^{48,49} Prior to this report, the Fu lab observed the proficiency of tridentate pybox ligands (e.g., **16**; Figure 3) to enable the room-temperature, nickel-catalyzed Negishi coupling of symmetrical secondary alkyl bromides and iodides.⁵⁰ It was postulated that the tridentate nature of pybox ligands prevented the undesired β -H elimination pathway, which would require a vacant coordination site. Reaction optimization facilitated the development of several asymmetric variations that generate challenging stereocenters applicable to complex molecule synthesis, as demonstrated in Fu's formal total synthesis of fluvirucinine A₁ (**17**), the aglycon of macrolactam antibiotic fluvirucin A₁ (**18**).⁵¹ A key nickel(II)-catalyzed asymmetric cross-coupling of racemic allylic chloride **9** and alkylzinc reagent **10** in the presence of (*S,S*)-**16** generated γ -disubstituted enone **11** in excellent yield and 96% ee. Elaboration over two steps to bromide **12**, followed by conversion to the alkylzinc and a second nickel(II)-catalyzed asymmetric Negishi cross-coupling with racemic allylic chloride **13**, provided ester **14** in good yield and >98% ee with a 15:1 diastereomer ratio (d.r.) A subsequent two-step conversion to aldehyde **15** intersects Suh's⁵² synthesis of fluvirucinine A₁ (**17**). This method exemplifies the efficiency of the $C(sp^3)-C(sp^3)$ cross-coupling and presents a creative solution to the particularly difficult challenge of remote stereochemical control.

At present, the majority of examples of this technology require a stabilizing group adjacent to the site of the putative carbon-centered radical. Eliminating this condition would further improve the utility of this asymmetric cross-coupling method. Additionally, stereogenic organometallic coupling partners (e.g., secondary alkylzinc reagents) have not yet been reported in this asymmetric transformation. A potential goal for this synthetic method would be combination of a racemic secondary alkyl halide and a racemic secondary alkylmetal reagent to form vicinal stereocenters along an alkyl chain with high levels of enantio- and diastereoselectivity.

Intramolecular Heck Cyclizations – Minfiensene

The asymmetric generation of all-carbon quaternary stereocenters represents a significant challenge in synthesis.⁵³ Since quaternary stereocenters are found in many natural product structures, convenient enantioselective methods for their formation would be useful. One such method is the Heck reaction,⁵⁴ wherein a palladium(0) catalyst promotes the vinylation of an aryl or vinyl halide or triflate. The large body of literature on palladium catalysis and mechanism,⁴¹ as well as an ever-growing collection of chiral ligands for transition-metal catalysis, greatly increased the potential of this method toward asymmetric catalysis. Additionally, an abundance of synthetic endeavors employing diastereoselective or non-stereoselective intramolecular Heck reactions have appeared,⁵⁵ increasing the significance of an enantioselective process. In 1989, the labs of Shibasaki⁵⁶ and Overman⁵⁷ independently reported the first variants of an intramolecular catalytic, asymmetric Heck reaction. Initial levels of enantioselectivity were moderate; however, subsequent optimizations realized good

to excellent selectivities in the generation of tertiary and all-carbon quaternary stereocenters.⁵⁸

Indole alkaloids comprise a large number of natural and pharmaceutical substances that possess a wide range of biological activities.⁵⁹ The plant alkaloid minfiensine (**22**, Figure 4) represents a compelling example of the all-carbon quaternary stereocenter motif in bioactive natural products. Minfiensine and related alkaloids have been used in traditional medicines and possess promising anticancer activity.⁶⁰ The intriguing polycyclic structure and biological relevance of minfiensine (**22**) prompted the Overman laboratory to explore a catalytic, enantioselective Heck reaction to generate the sole quaternary stereocenter at C(9a).⁶¹ It was discovered that the palladium-catalyzed intramolecular Heck reaction of dienyl aryl triflate **19** in the presence of phosphinooxazoline ligand (*S*)-**23** under microwave conditions produced indoline **20** in good yield 99% ee. Subsequent acid promoted carbamate cyclization produced the tricyclic core of minfiensine (i.e., **21**) that was then elaborated to the natural product. The efficiency and selectivity of the catalytic, asymmetric Heck reaction facilitated completion of the target, where the remaining stereocenters are derived from this initial transformation.

Despite numerous examples of the asymmetric Heck reaction in total synthesis,⁵⁸ there are several features that could be improved in the coming years. Reactions typically require high temperatures and somewhat high catalyst loadings, and the development of chiral ligands that greatly increase the reactivity of the transition metal while maintaining an adequate asymmetric environment would be greatly beneficial. Since most enantioselective Heck reactions employ an sp²-hybridized organohalide component, another frontier lies in the application of unactivated alkyl carbon electrophiles that possess β-hydrogens in both intramolecular and intermolecular cases, and area currently in its infancy.⁶²

Indole Friedel–Crafts Alkylations – Flustramine B

Numerous methods have been developed for the generation of substituted indoles,^{63,64} however, enantioselective indole functionalization is far less explored. To address the deficiencies in the indole functionalization literature, Jørgensen⁶⁵ and MacMillan⁶⁶ independently developed strategies for asymmetric Friedel–Crafts alkylation of conjugate acceptors with electron-rich heteroaromatics in 2001. The method of MacMillan employs secondary amine catalyst **28** (Figure 5) that facilitates the LUMO-lowering activation of α,β-unsaturated aldehydes for a variety of transformations.^{67,68} Although imidazolidinone **28** was a sufficient catalyst for the Friedel–Crafts alkylation of pyrroles with good yields and excellent enantioselectivities,⁶⁶ application of less-activated indole substrates resulted in sluggish reactivity with considerably diminished selectivities.⁶⁹ Kinetic investigations of iminium-catalyzed reactions revealed that the overall reaction rate was influenced by the efficiency of formation for both the iminium ion and C–C bond, prompting the development of a modified imidazolidinone catalyst (**29**). This refinement minimized the steric bulk around one face of the catalyst, thereby exposing the nitrogen lone-pair. This structural change translated into increased reactivity that enabled the asymmetric Friedel–Crafts alkylation of a variety of indoles in good to excellent yields with very high enantioselectivities.⁶⁹

Pyrroloindoline alkaloids represent a family of polyindole alkaloids of diverse structural complexity and biological relevance.⁷⁰ Diastereoselective syntheses of this core have focused on the control of the C(3a) all-carbon quaternary stereocenter as a key design element.^{71,72,73} With a powerful and mild indole alkylation method in hand, MacMillan and coworkers devised a cascade strategy for the catalytic, asymmetric preparation of the C(3a) stereocenter and the pyrroloindoline core of potassium-channel blocker (–)-flustramine B (**27**) in one step.⁷⁴ In this key transformation, tryptamine derivative **24** and acrolein, in the presence of catalyst **29**, underwent the asymmetric Friedel–Crafts alkylation to provide iminium intermediate **25**.

Subsequent carbamate cyclization and hydrolysis to regenerate the catalyst provided the core (**26**) in good yield and 90% ee. Importantly, this enabled completion of (–)-flustramine B (**27**) in just 6 steps and good overall yield and highlights the efficiency of this cascade approach. It is noteworthy that this strategy is not reserved for the pyrroloindoline architecture, but also has potential for application to various polycyclic indolines such as the diazonamide family of cytotoxic alkaloids.⁷⁴ It is interesting to note the capacity of both the intramolecular Heck reaction (vide supra) and indole Friedel–Crafts alkylation to generate similar indoline structural motifs despite the drastically different bond-connecting strategies. The success of these dissimilar strategies allows for a great deal of flexibility in synthetic planning.

Although iminium activation methods with chiral amine catalysts have been successful for numerous transformations, catalyst loading, turnover frequency, and excesses of certain reagents limit the large-scale industrial application of these methods. Additionally, in some cases the organic catalyst may be more difficult to remove from the reaction products than a metal catalyst. However, the typically air- and moisture-stable reaction conditions, low cost of some catalysts, and often metal-free conditions are attractive. The variety of asymmetric transformations (some proceeding through substantially different reaction pathways) realized with chiral amine catalysts to date indicates a burgeoning field of useful enantioselective catalysts.

Pictet–Spengler Cyclizations – Harmicine

Since the intramolecular cyclization of an aromatic ring onto an iminium species was reported by Pictet and Spengler in 1911,⁷⁵ the transformation has been of great use in the synthesis of many important alkaloid natural products.⁷⁶ Indeed, the need for asymmetric variants of this reaction was recognized and several diastereoselective protocols have been devised.⁷⁶ A common approach to diastereoselective Pictet–Spengler cyclization has been to employ tryptophan derivatives to control the stereochemistry of the cyclization. However, such a technique in the synthesis of a natural product such as the anti-leishmania compound harmicine (**35**; Figure 6) necessitates the removal of the stereocontrol element at C(5) following the diastereoselective cyclization. Nonetheless, Allin and coworkers proved this a method viable method in 2007.⁷⁷ This particular structure, however, highlighted a challenge for enantioselective catalysis and an opportunity to improve synthetic efficiency.

When considering prospects for asymmetric induction, Jacobsen and Taylor considered activated *N*-acyliminium ions as a template and reasoned that a chiral thiourea derivative might be effective in promoting cyclization. In practice these Brønsted acids,⁷⁸ as well as other Brønsted acids investigated later by other groups,^{79,80} proved to be excellent catalysts for enantioselective indole annulations with in situ generated *N*-acyliminium species (e.g., **33**). In later studies by Jacobsen and coworkers it was found that hydroxylactams (e.g., **31**) are convenient precursors to *N*-acyliminium ions and in turn enabled access to various polycyclic structures.^{81,82} With this effective protocol in hand, an efficient catalytic asymmetric synthesis of harmicine (**35**) was realized in four steps from tryptamine (**30**). Several mechanistic experiments have suggested that asymmetric induction is controlled by a complex of the Brønsted acid catalyst (**32**) and a chloride counterion closely associated with the iminium ion (e.g., **33**) that effectively blocks approach to one face of the electrophile. This insight into the remarkable mechanism of this transformation has led to a related C–C bond forming process employing oxocarbenium ions.⁸³ Further exploitation of this unusual proposed catalyst/anion interaction could lead to a variety of other asymmetric addition reactions, for example, intermolecular alkylation *N*-acyl iminium ions. Paralleling the history of the Diels–Alder reaction (vide supra), the exploration of the Pictet–Spengler cyclization has provided a useful method to access many heterocyclic structures embedded in alkaloid natural products using a classical reaction with well-established synthetic applications.

Phase Transfer Alkylations – Indacrinone

Enolate alkylations exemplify the fundamental utility of the carbonyl group for C–C bond formation. Strategies to induce asymmetry in these reactions have included chiral auxiliaries and chiral ligands, although few examples are catalytic. A particularly challenging class of product targets are all-carbon quaternary stereocenters adjacent to carbonyl groups. One example of an important target bearing this motif is the diuretic drug candidate indacrinone (**40**, Figure 7).⁸⁴ Given the lack of efficient methods for synthesizing this structure, researchers at Merck envisioned an enantioselective phase transfer alkylation method based on a quaternary ammonium salt derived from a naturally occurring cinchona alkaloid (e.g., **37**). In the event, readily prepared indanone **36** was methylated in 95% yield and 92% ee and then converted to indacrinone (**40**) in three additional steps. Although successful in achieving enantioselective enolate alkylation, the mechanism of this process appears to be very complicated;⁸⁵ however, enantiofacial selectivity in the alkylation event may be rationalized through hypothetical transition state **38**. Three key interactions are thought to control selectivity: a hydrogen bond between the enolate oxygen and the catalyst hydroxyl group, and two π -stacking interactions between the four aromatic rings. Perhaps a consequence of the complex mechanism, the substrate scope for enolate alkylation is unfortunately limited and other solutions to this problem are still necessary. However, these initial results have led to several related catalytic enantioselective reactions employing cinchoninium salts or related organic ammonium complexes as catalysts.⁸⁶ The discovery of these useful catalysts has provided not only an alternative to related transformations using metal catalysts, but also a means of accessing chiral environments that are simply not possible with metal-based catalysts. Moreover, eliminating metal waste materials is attractive from an industrial and environmental standpoint. Ultimately, the studies directed toward an enantioselective synthesis of indacrinone (**40**) demonstrate the versatility of privileged catalysts developed for the synthesis of target molecules for a range of other applications.

Pd-Catalyzed Enolate Alkylation – Cyanthiwigin F

A recent case of enantioselective enolate alkylation is the synthesis of the cytotoxic marine natural product cyanthiwigin F (**48**, Figure 8). The cyanthiwigin family is composed of over thirty diterpenoids, most of which bear two quaternary stereocenters, at C(6) and C(9), and a *syn*-relationship of the methyl groups in the central ring. These central stereochemical elements are a complicating factor for a convergent strategy that might seek to couple the five- and seven-membered ring portions and subsequently form the six-membered ring. To avoid this difficulty, Enquist and Stoltz chose instead to address these two central stereocenters at an early stage and append the five- and seven-membered rings to the assembled cyclohexane. Accordingly, a synthetic strategy was devised that involved a one-pot, double-enantioselective enolate alkylation reaction to simultaneously form both quaternary stereocenters. Although such enantioselective alkylations have proven difficult, recent research in the Stoltz laboratories and others had identified palladium-catalysts that may provide a solution to this problem and enable the synthesis of a variety of targets containing quaternary carbon stereocenters, including the cyanthiwigins.^{87,88}

The implementation of this plan began with a Claisen–Dieckmann sequence that converted diallyl succinate (**41**) to bis(β -ketoester) **42** as a 1:1 mixture of racemic and meso diastereomers. Upon exposure to the catalyst derived from Pd(dmdba)₂ and phosphinooxazoline ligand (*S*)-**23**,^{89,90} were transformed to bis(allylated) ketone **43** in 75% yield and 99% ee as a 4.4:1 mixture of diastereomers. With both quaternary centers in place, elaboration of this stereochemically rich core structure to the natural product was achieved in six further steps. Enol triflate formation and Negishi coupling preceded a tandem ring-closing metathesis/cross-metathesis sequence with Grubbs' ruthenium catalyst **45**. Aldehyde-olefin radical cyclization

generated the final ring of the cyanthiwigin core (i.e., **47**), and enol triflate formation and palladium-catalyzed cross-coupling formed (–)-cyanthiwigin F (**48**). Choosing to confront the difficult stereochemical elements of the cyanthiwigin structure at an early stage led to a direct synthetic route proceeding in nine steps from diallyl succinate (**41**). The strategy herein was enabled by the intriguing reaction mechanism of the enantioselective decarboxylative allylation, in which all three stereoisomers of bis(β-ketoester) **42** are selectively converted to a particular stereoisomer of product (**43**) with high selectivity through a stereoablative process.⁹¹ Additionally, of the nine steps required for the synthesis, seven form C–C bonds, and four of these steps form *multiple* C–C bonds. Directly addressing the carbon-framework of the target molecule and the stereochemical challenges embedded within ultimately lead to an efficient synthetic sequence to this important molecule.

At this time, the proposed chiral palladium enolate has been intercepted by allyl or proton electrophiles.⁸⁹ Although the synthesis of cyanthiwigin F (**48**) demonstrates the versatility of allyl moieties for further derivatization, the direct use of alternative electrophiles would provide a more general and direct method for transition metal-mediated enolate functionalization.

Trimethylenemethane Cyclizations – Marcfortine B

Of the many fundamental approaches to the formation of five-membered rings from acyclic precursors, the [3 + 2] cycloaddition is among the most convergent strategies. A useful method of achieving such a cyclization is via a trimethylenemethane (TMM) intermediate.⁹² This interesting non-Kekulé molecule was first prepared and studied by Dowd and coworkers through photolytic decomposition of a cyclic diazene precursor. However, the free diyl is prone to several undesired reaction pathways and does not lend itself to asymmetric catalysis. Despite this, intramolecular diyl trapping reactions are valuable methods of cyclopentane formation.⁹² Recognizing the synthetic utility of TMM, Trost and coworkers developed an array of 2-(trimethylsilyl)-2-propenyl acetate reagents that generate a metal•TMM complex when exposed to a palladium catalyst.^{93,94} A recent application of this transformation in total synthesis is the approach to marcfortine B (**55**; Figure 9a), a member of a family of anti-parasitic agents, by Trost and coworkers.⁹⁵ The strategy employed sought to forge the [2.2.2]bicycle via an intramolecular radical cyclization, and install the spiro all-carbon quaternary stereocenter by the cycloaddition of oxindole **50** with TMM precursor **51**. In the event, an excellent yield was observed for the annulation reaction yielding spirooxindole **52** as a 1:1 mixture of diastereomers. Over the course of nine additional steps, spirocycle **52** was transformed into amide **53**. Preparation of the xanthate derivative of alcohol **53** enabled radical cyclization generating the challenging [2.2.2]bicycle **54**. Seven further steps produced (±)-marcfortine B (**55**).

Although this strategy demonstrated several intriguing ring-forming reactions, an asymmetric synthesis of **55** would require an enantioselective variant of the key TMM-[3 + 2] cycloaddition, a goal that has remained elusive.⁹⁶ Ito and coworkers reported the first asymmetric [3 + 2] cycloaddition with various bis(phosphine) ligands, but observed only moderate enantiomeric excess (up to 78%) and diastereomeric ratio (up to 4:1 trans:cis).⁹⁷ Thereafter, Trost and coworkers explored bulky monodentate phosphoramidite ligands (e.g., (*R,R,R*)-**59**) for the transformation and observed very high enantioselectivity for the first time (Figure 9b).^{98,99,100} Of particular interest is the enantioselective addition of substituted TMM reagents to functionalized oxindole derivatives.⁹⁹ The use of oxindole **56** and TMM-precursor **57** in the palladium-catalyzed cyclization with ligand (*R,R,R*)-**59** yielded spirooxindole **58** with 14:1 d.r. and 96% enantiomeric excess for the major diastereomer. Although a completed asymmetric synthesis of marcfortine B (**55**) from intermediate **58** has not been reported, many of the key functional groups are in place and the challenging spiroquaternary stereocenter has been installed (cf. **52** and **58**). The development of this valuable asymmetric transformation

highlights the ongoing efforts to devise new and useful techniques toward construction of important molecules.

Conclusion

The representative synthetic efforts presented herein demonstrate the critical interplay between target-directed synthesis and the development of novel reaction methodology. Although many useful asymmetric technologies are currently available, the specific challenges posed by important natural product and pharmaceutical compounds highlight deficiencies in the current technology. Envisioning strategies to construct these relevant molecules through means beyond the current arsenal of enantioselective transformations will facilitate the evolution of both synthetic planning and reaction development. The symbiotic relationship between total synthesis and method development can continue to expand the understanding of synthetic strategy and catalysis on both fundamental and practical levels.

Despite the substantial advances realized to date, significant challenges remain for both multi-step synthesis and catalysis. In addition to enhancements to efficiency and selectivity, better reactivity and handling stability are continually required to implement and improve industrial processes for existing methods. Exceptionally reliable methods will aid in the discovery of new bioactive compounds through high-throughput combinatorial screening techniques that are well established in the pharmaceutical industry, but relatively limited by the number of readily accessible chiral building blocks. Existing methods may be improved by identifying systems with better functional group tolerances that might obviate the need for protecting and masking groups. Similarly, known privileged chiral frameworks may be modified to more effectively control chiral space for especially challenging transformations, a technique conspicuously successful for Trost's TMM cyclizations.

Creative solutions are required to address specific organic transformations that remain significant impediments to efficient syntheses, namely: formation of multiple stereocenters and rings, formation of multiple C–C bonds, generation of vicinal quaternary stereocenters, and C–H and C–C functionalization reactions. Cyclic structures often present particular challenges due to the unique strain and steric elements imparted by their connectivity. As a result, many highly strained or complex polycyclic structures are daunting targets for synthesis. Finally, the disclosure of new natural product possessing novel structures will serve to identify new and different challenges for synthetic chemistry and catalysis.

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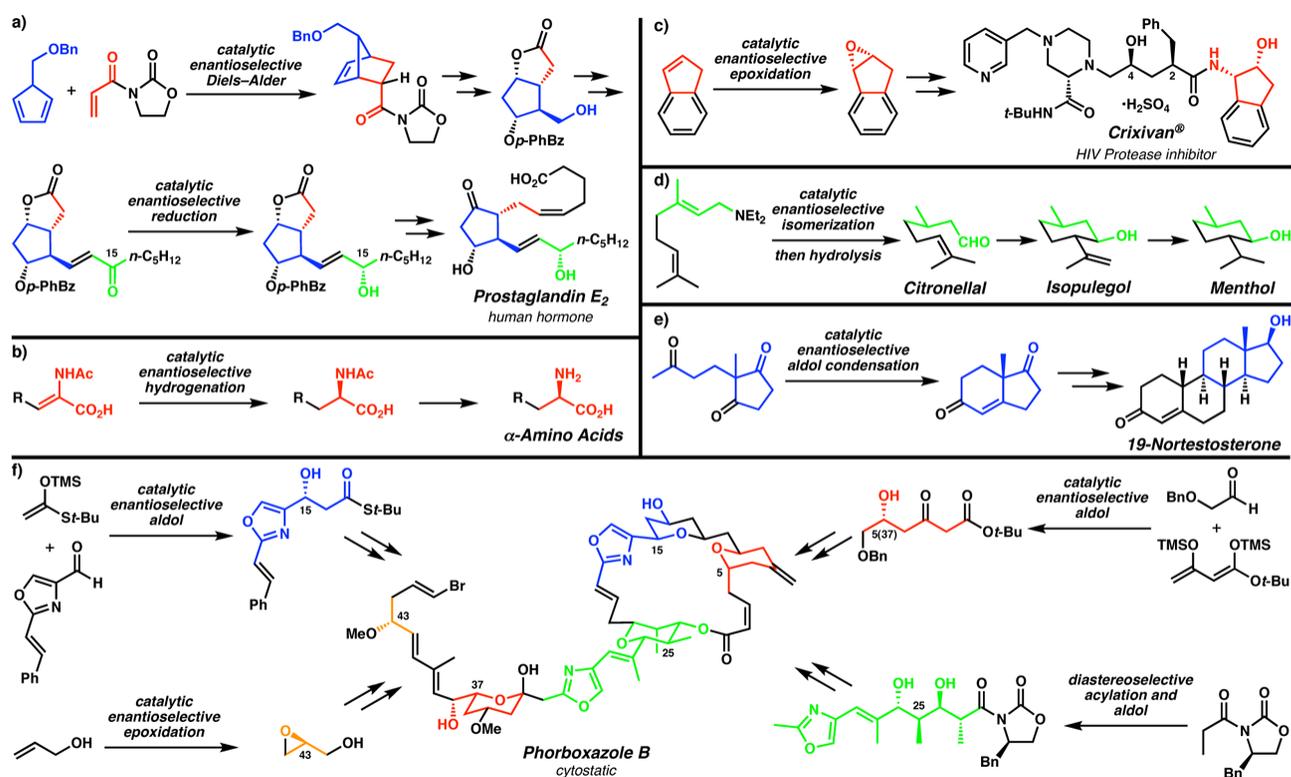


Figure 1. Selected examples of enantioselective catalysis in total synthesis

Natural products and pharmaceuticals often possess challenging structural features and functionalities, particularly stereochemical elements. (a) Corey's synthesis of prostaglandin E₂ utilizing an asymmetric Diels-Alder reaction¹³ and carbonyl reduction.¹⁶ Various industrial applications, including (b) the asymmetric hydrogenation toward α -amino acid building blocks,¹⁹ (c) the asymmetric epoxidation toward Merck's HIV protease inhibitor Crixivan[®],²⁰ and (d) the asymmetric isomerization of allylic amines en route to commodity chemicals,²¹ have explored the limits of catalysis and efficiency to minimize cost. The asymmetric construction of C-C bonds, apparent in (e) the amino acid-catalyzed intramolecular aldol condensation toward important steroid building blocks,²⁷ and (f) various enantioselective intermolecular aldol reactions toward fragments of the cytostatic agent phorboxazole B,²⁸ maximize the use of stereochemical information of precious intermediates through convergency. (Reduced to 45%)

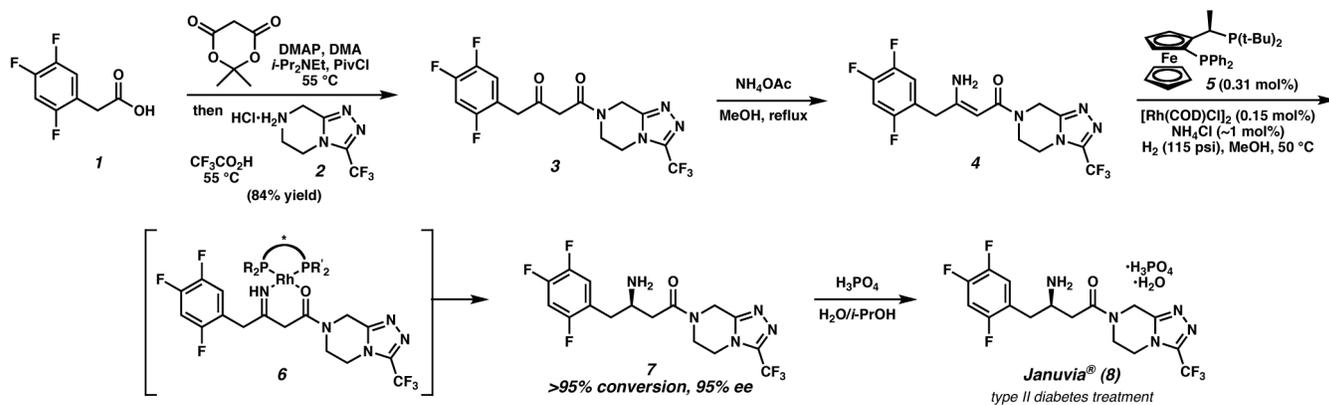


Figure 2. Asymmetric hydrogenation of β -enamino amides toward Januvia® (8)

The rapid and selective synthesis of β -enamino amide 3 enabled a key rhodium/5-catalyzed enantioselective hydrogenation under mildly acidic conditions to directly reveal the β -amino amide in Merck's synthesis of Januvia®, an FDA-approved treatment for type II diabetes.^{36, 39} DMAP, 4-(*N,N*-dimethylamino)pyridine; DMA, *N,N*-dimethylacetamide; PivCl, pivaloyl chloride; COD, cyclooctadiene. (Reduced to 45%)

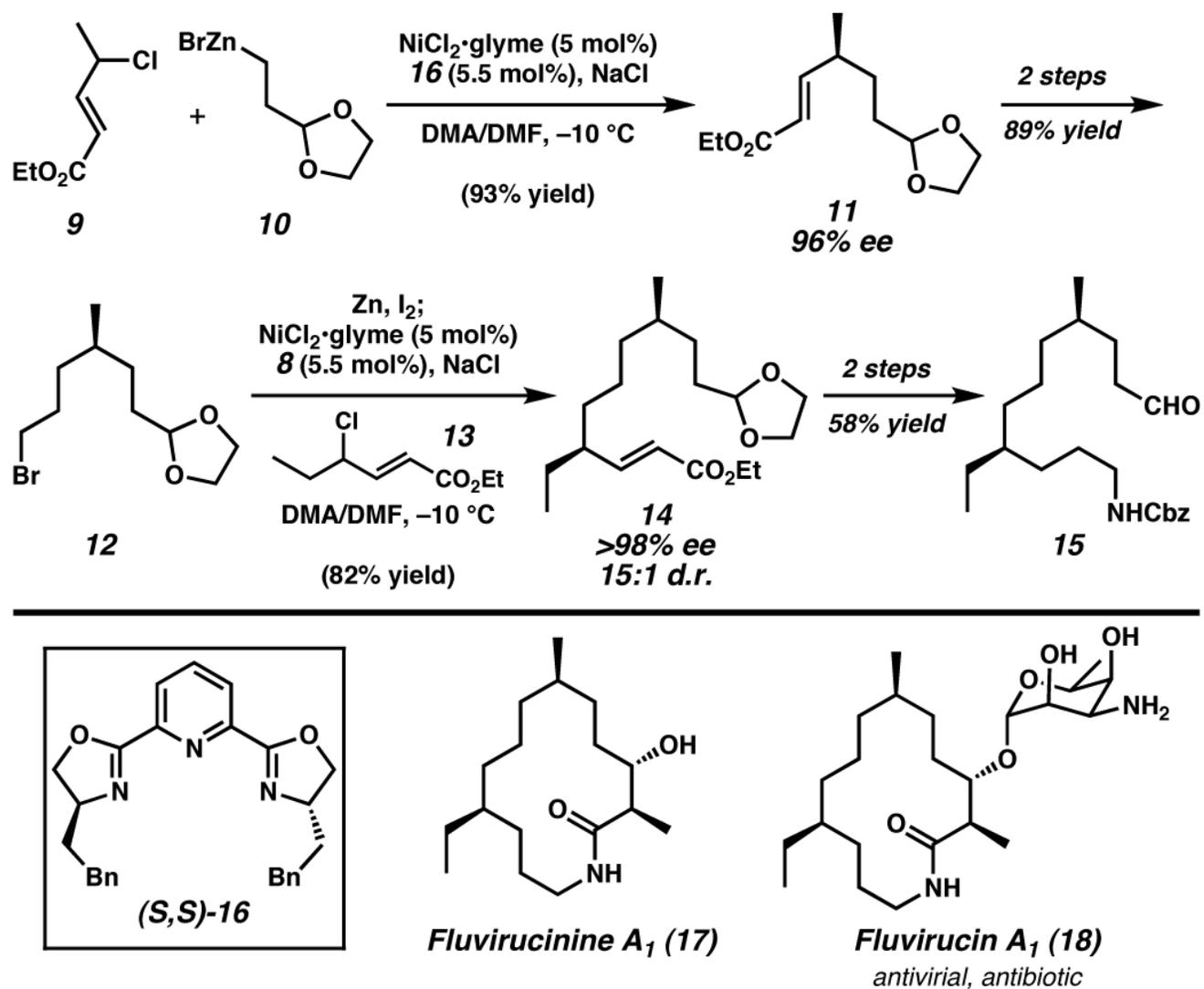


Figure 3. Enantioselective C(sp³)-C(sp³) cross-coupling toward fluvirucinine A₁ (17)
 Sequential asymmetric C(sp³)-C(sp³) Negishi cross-couplings of racemic allylic chlorides and alkylzinc reagents catalyzed by nickel/(S,S)-16 enabled the rapid formal synthesis of Fluvirucinine A₁ with excellent enantio- and diastereoselectivity, highlighting a creative solution to remote stereochemical control in unfunctionalized systems.⁵¹ Glyme, 1,2-dimethoxyethane; DMF, *N,N*-dimethylformamide. (Reduced to 45%)

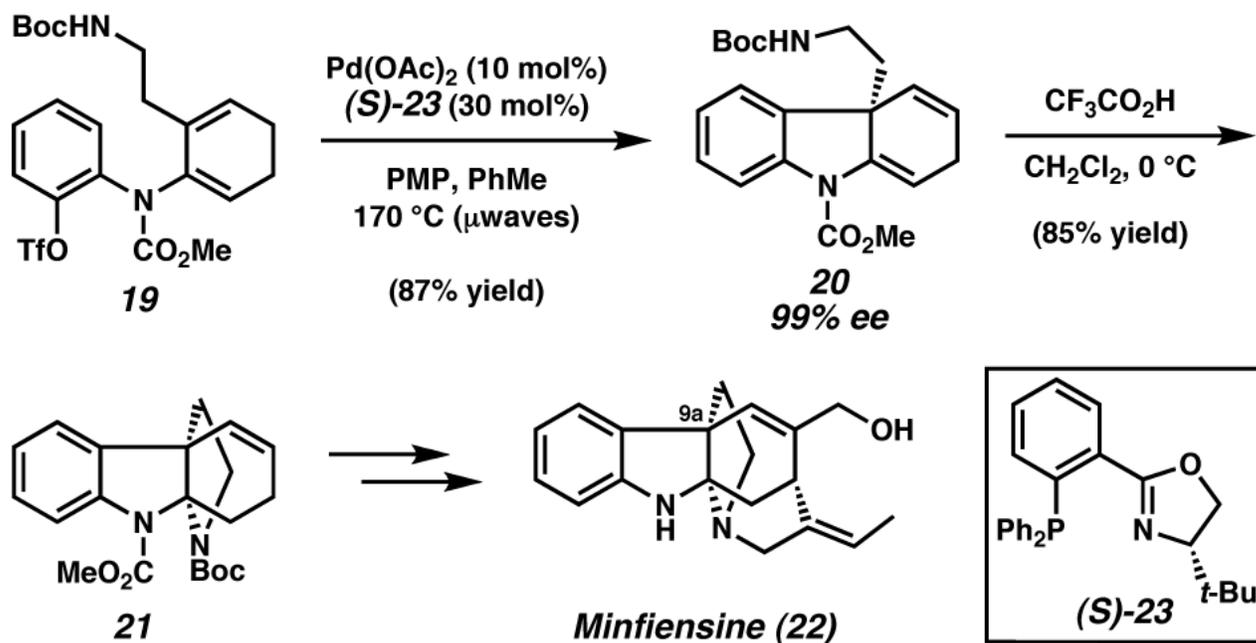


Figure 4. Asymmetric Heck cyclization toward minfiensine (22)

The palladium/**23**-catalyzed enantioselective intramolecular Heck cyclization of **19** forged the C(9a) all-carbon quaternary stereocenter, and upon acid-mediated cyclization, the polycyclic core of minfiensine. The application of this method allowed the diastereoselective preparation of the remaining stereocenter and completion of the alkaloid.⁶¹ PMP, 1,2,2,6,6-pentamethylpiperidine. (Reduced to 45%)

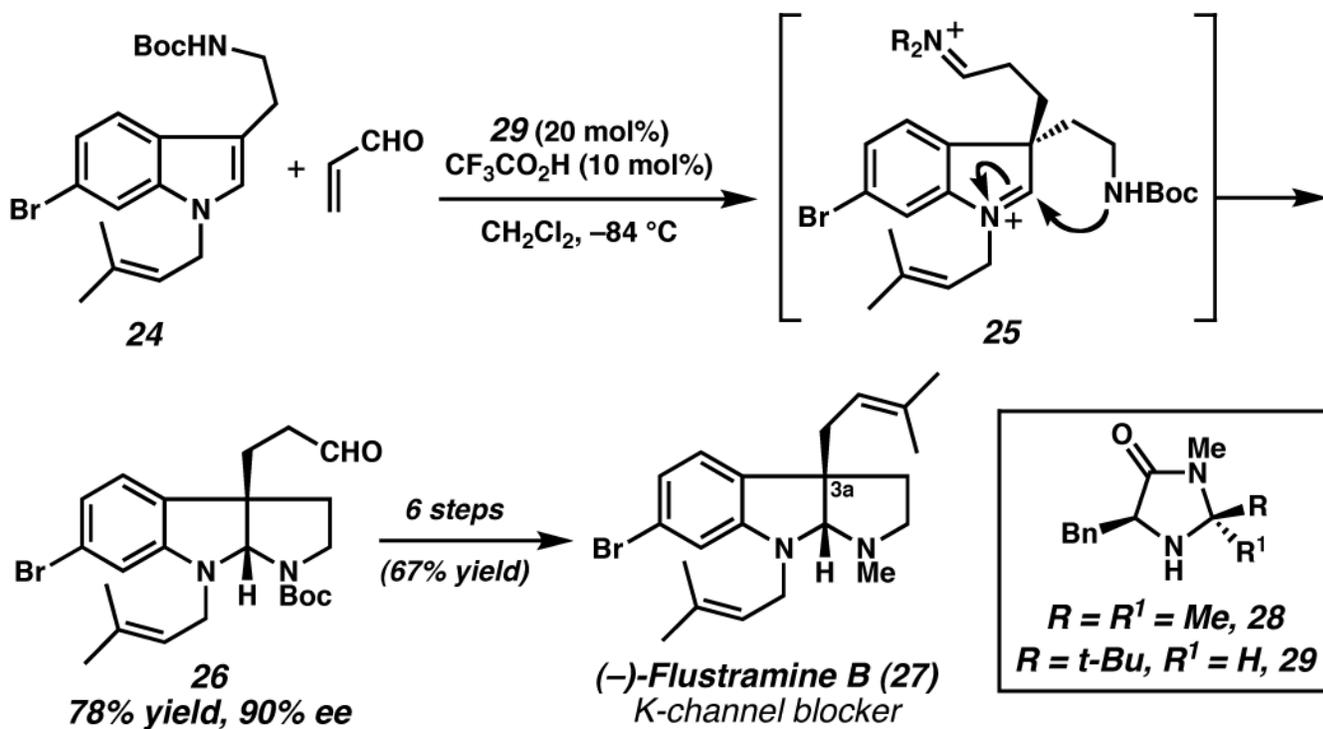


Figure 5. Amine-catalyzed indole alkylation toward flustramine B (27)

The enantioselective C(3a) alkylation of tryptamine derivative **24** catalyzed by amine **29**, upon subsequent intramolecular cyclization, provided the pyrroloindoline core of (-)-flustramine B. This selective cascade process prepared the all-carbon quaternary stereocenter rapidly and efficiently enabling completion of this K-channel blocker.⁷⁴ (Reduced to 45%)

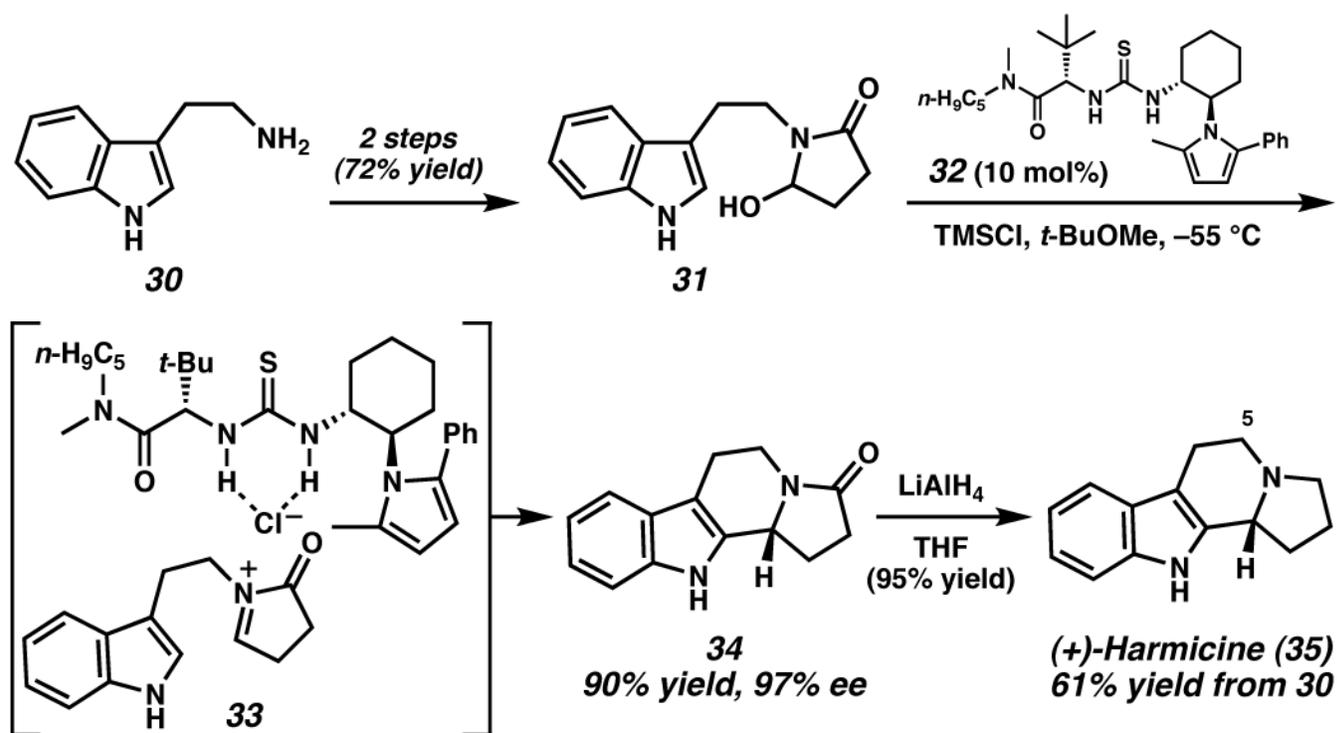


Figure 6. Enantioselective Pictet–Spengler cyclization toward harmicine (35)

Facile preparation of hydroxylactam **31** facilitated the asymmetric Pictet–Spengler cyclization catalyzed by thiourea **32**. The enantioselective *N*-acyl iminium ion cyclization enabled rapid construction of the alkaloid (+)-harmicine following this key transformation.⁸¹ TMSCl, chlorotrimethylsilane; THF, tetrahydrofuran. (Reduced to 45%)

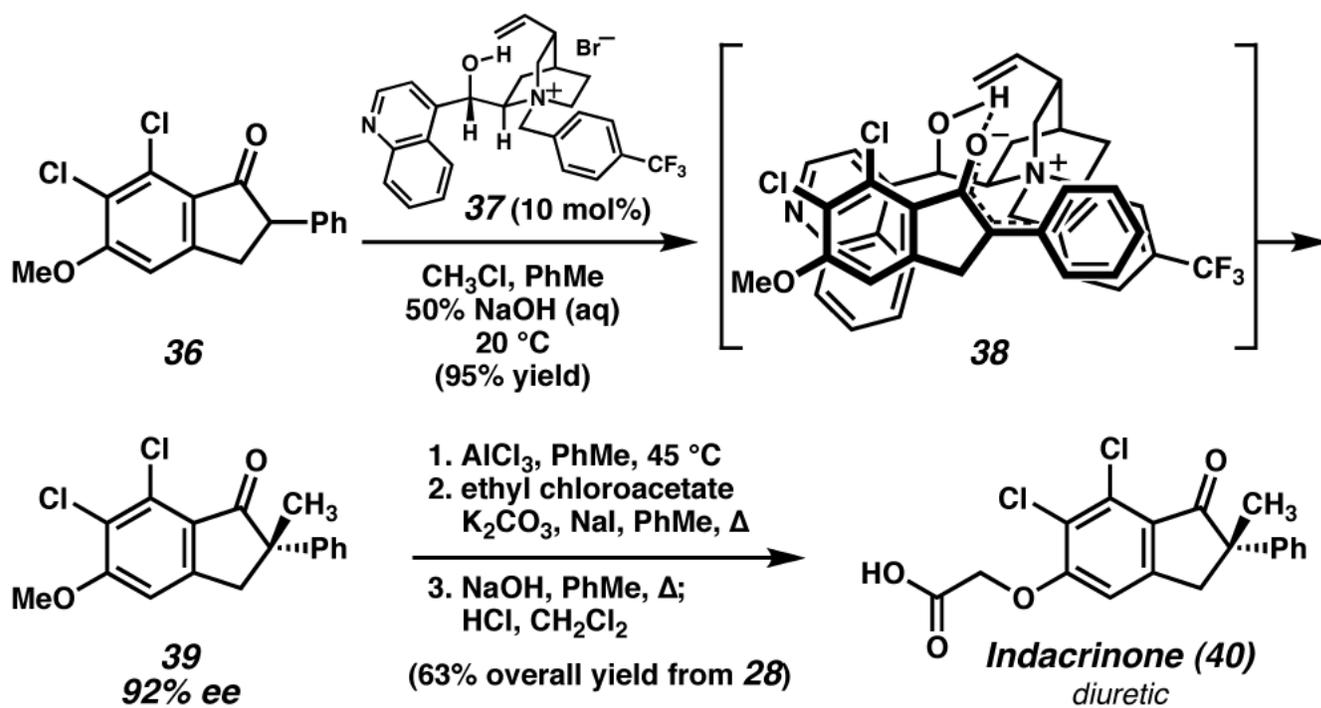


Figure 7. Asymmetric phase-transfer alkylation toward indacrinone (40)

Merck scientists developed an enantioselective alkaloid salt-catalyzed phase-transfer enolate alkylation to gain access to indanone **39** with excellent stereoselectivity en route to the diuretic drug candidate indacrinone.⁸⁴ (Reduced to 45%)

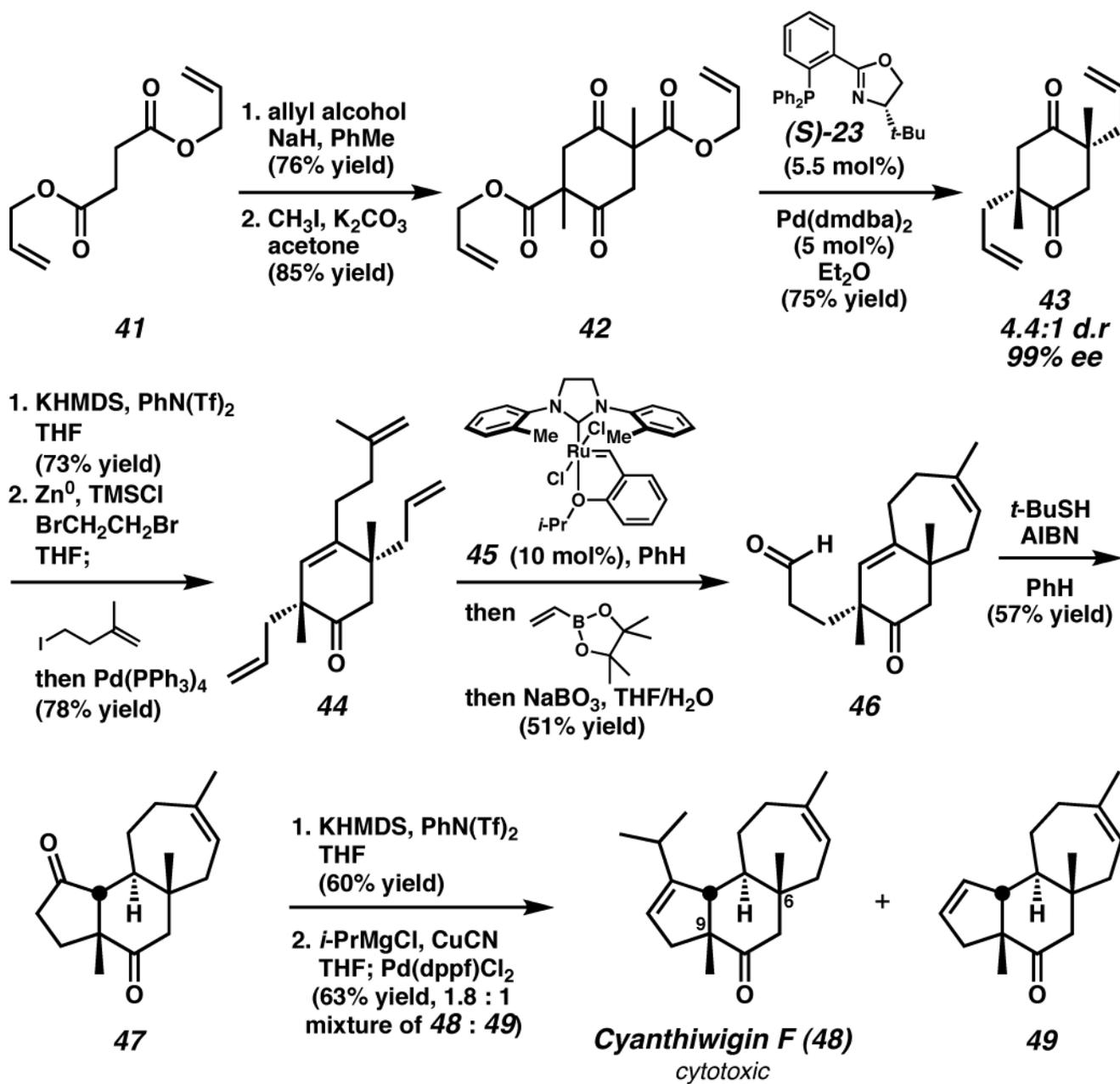


Figure 8. Double enantioselective enolate alkylation and the synthesis of cyanthiwigin F (8)

Preparation of a diastereomeric mixture of racemic and meso β -ketoester **42** allowed the strategic application of the palladium/(*S*)-**23**-catalyzed double enantioselective enolate alkylation to generate both all-carbon quaternary stereocenters of **43** with excellent stereoselectivity. A subsequent Negishi coupling, ring-closing metathesis, and radical-mediated aldehyde-olefin cyclization rapidly constructed the tricyclic core of cyanthiwigin F, completing a synthesis highlighted by several steps that involve the generation of multiple C–C bonds.⁸⁷ dmdba, bis(3,5-dimethoxybenzylidene)acetone; KHMDS, potassium bis(trimethylsilyl)amide; PhN(Tf)₂, phenyl bis(trifluoromethane)sulfonimide; AIBN, 2,2'-azobis(isobutyronitrile); dppf, 1,1'-bis(diphenylphosphino)ferrocene. (Reduced to 45%)

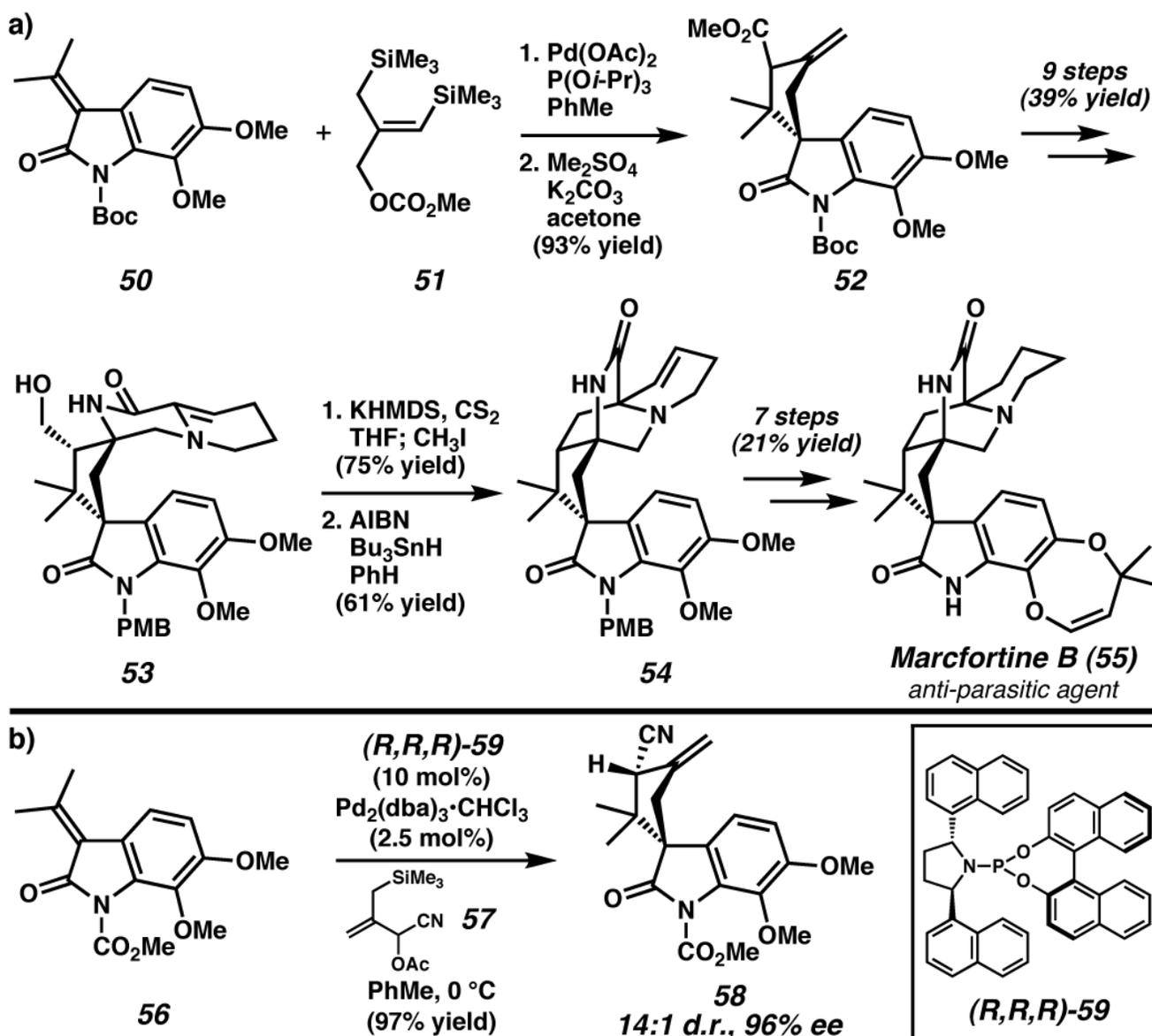


Figure 9. Enantioselective trimethylenemethane [3 + 2] cyclization toward marcfortine B (55)
 (a) The palladium-catalyzed trimethylenemethane [3 + 2] cyclization of oxindole **50** prepared cyclopentane **52** in excellent yield. Elaboration to tetracycle **53** facilitated an intramolecular radical cyclization to synthesize the core of marcfortine B, which was completed in seven additional steps.⁹⁵ (b), The recent development of enantioselective palladium-catalyzed TMM cyclizations with (*R,R,R*)-**59** allows access to spiro-annulated products such as **58** with high diastereo- and enantioselectivity.⁹⁹ The potential application to marcfortine B has not yet been realized. Boc, *tert*-butoxycarbonyl; dba, bis(benzylidene)acetone. (Reduced to 45%)